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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,422	05/09/2001	Xianxhang Yu	035879-0122	2132

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	21

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,422	YU ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2003 and 12 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *6,7 and 10-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8, 9, 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed on 08-19-2003 and supplemental response filed on 9-10-2003 are acknowledged. Claims 2, 3, and 5 are amended, and claims 20-22 are new.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Election/Restrictions

Claims 6, 7, 10-19 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) for reason of record.

This application contains claims 6, 7, and 10-19 drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-22 are pending and claims 1-5, 8, 9, 20-22 are under consideration as they are drawn the elected species, amoebapore.

Claim Objections

Claims 3 and 4 remain objected, and the new claims 20, and 22 are also objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The objection of claim 5 is withdrawn because the amended claim is no longer drawn to the unmodified naturally occurring amoebapore peptide.

Applicant argues claims 3 and 4 recite preferred pore-forming cytolytic peptides and they depend from claim 1, which recites a protcytotoxin containing a modified cytolytic peptide. The argument is fully considered but found not persuasive because the base claim 1 is drawn to a modified peptide only, but the species in the objected claims are drawn to a unmodified, naturally occurring "amoebapore" peptide. Amoebapores in claim 3 and 4 are not "a cytotoxic peptide having at least one lysine residue bound via a peptide bond". Compare the species in the non-objected claim 8 and the species in claims 3 and 4.

If the base claim says "a cytotoxic peptide derivatized to produce a derivative having at least one lysine residue bound at a lysine residue of said cytotoxic peptide..." to reflect that there are two parts in the base claims, and "amoebapores" in the objected claims further limit a naturally occurring part of the base claim before derivatization would obviate the objection. This suggestion is how to further limit "amoebapores". However, applicant's attention is drawn to "derivatives" in the dependent claims 3 and 4, which is not a naturally occurring cytotoxic peptide. The Office at this point is not clear how Markush language could be used to claim "derivative" and "amoebapores" as an alternative because one is already derivatized and the other has to be derivatized. They are not structural alternative.

The Office did not object claim 2 because the limitation "a pore-forming cytotolytic peptide" has been interpreted as the peptide of claim 1, which can make a hole in a cell and dissolve or disintegrate said cell: not structural element is present in claim 2.

Specification

The objection of disclosure at paragraph [0071] is **withdrawn** since the amendment corrected the defect.

Claim Rejections - 35 USC § 112

Claims 3 and 4 remain rejected for reason of record and claims 20 and 21 are also under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claim 3 still recites "amoebapore...and analogs and derivative thereof". Applicant argues one of skill in the art would know what is meant by an analog and derivative, and the specification at page 10 paragraph [0028-0029] provides "cytotoxic peptides may be modified or derivatized to produce analogs and derivatives..." and "amoebapore alanogs are non native forms never before known in nature, based on the observed homologies and known structure and properties of the native protein...". Applicant argument appears to indicate amebapore analogs" are fragments of a known amoebapore. However, based on pages 10-11 of the specification, there appears to be no difference between "analogs" and "derivatives", both modified peptide by substitution, addition, etc.

Further applicant's attention is directed to "**and** analogs **and** derivative'. A proper Markush group is the format used in instant claim 4.

Further, applicant's response that "amoebapore", is alternative of "amoebapore derivatives" which further limit "procytotoxin" of base claim does not make much sense.

How could something not modified (amoebapore in claim 3) further limit something modified (claim 1 and 2)? Note claims objection above.

Claim 4 remains also rejected for reason of record and also for the same reason as above in claim 3.

Claims 20 and 21 recite "amoebapore" but it is not clear whether it encompasses only naturally occurring protein i.e. the full-length protein as well as fragment thereof. Does it also include analogs or derivative? What is the relationship between the product in the base claims and "amoebapore" in the dependent claim. It appears that the product in base claims are modified or derivatized peptide but the products in the instant claims are fragment and/or naturally occurring protein without any modification.

Claim Rejections - 35 USC § 102

Claims 3 and 4 remain rejected for reason of record, and claims 20 and 21 are also rejected under 35 U.S.C. 102(b) as being anticipated by either Leippe et al (A5 of IDS, Paper No. 15, 1994, Proc. Natl. Acad. Sci. USA, vol. 91, pages 2602-2606) or Andra et al (A6 of IDS, Paper No. 15, 1996, FEBS Letters, vol. 385, pages 96-100). The rejection of claim 5 35 U.S.C. 102(b) is withdrawn because applicant removed the limitation "unmodified" from the claim.

The claims are interpreted as unmodified amoebapore peptide for the reasons given in the claim objections above.

Applicant argues that the claims are not drawn to the unmodified peptide but this argument is treated as argument not commensurate in scope of the claims.

Claim Rejections - 35 USC § 103

Claims 1-5, 8, and 9 remain rejected for reason of record and claim 22 is also rejected under 35 U.S.C. 103(a) as being unpatentable over either Leippe et al or Andra et al as applied to claims 3-5, 20, and 21 above, and further in view of Pinto et al (A11 of IDS, Paper No. 15, 1999, The Prostate Journal, vol. 1, pages 15-26), WO 97/33908 (A2 of IDS, Paper No. 15, 1997), and Liu et al (1979, Endocrinology, vol. 104, pages 962-966, abstract only).

This rejection is based on the Office interpretation of the claimed invention as the first product in claim 8 i.e. amoebapore H3 domain modified by linking two gamma linked glutamates through epsilon group of the C-terminal lysine.

Applicant's arguments filed 08-19-2003 and 09-15-2003 have been fully considered but they are not persuasive. Applicant argues for two main points: no suggestion to combine and hindsight reasoning. Applicant in the supplemental response filed on 09-12-2003 argues that Pinto et al uses MTX as the backbone molecule and instant application uses lytic peptide, thus Pinto does not teach or suggest to add poly-gamma-glutammate for peptide inactivation on the basis of charge neutralization: Nowhere in Pinto teaches neutralization of the instantly peptide.

In response to applicant's argument that there is no suggestion to combine the references, examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, WO 97/33908 teaches at page 3 line 15 to page 4 line 5 that there are great interest to use lytic peptides in the cancer treatment art but the use of such lytic peptides in cancer treatment has been limited because the peptides are also toxic to normal cells, and teaches the need for inactivating the lytic peptides until they reach cancer cells.

Leippe et al at page 2603 teach the positive charge at the C-terminal end, especially having lysine residue is important for the toxic lytic activity of the lytic peptide used in the instant application. Therefore, combination of WO 97/33908 and Leippe et al gives one in skilled art to modify the lysine residue most responsible for the amoebapore H3 domain as being "a pore-forming cytolytic peptide" such that the a pore-forming cytolytic peptide is inactivated until it reaches cancer cells. Neither WO 97/33908 nor Leippe et al teaches adding poly-gamma glutamates

However, Pinto et al teach at pages 22 and 23 teach how one skilled in art would modify the a pore-forming cytolytic, amoebapore H3 peptide in order to minimize damage to normal cells: the reference teaches that poly-gamma glutamates removing activity of PSMA, highly expressed in prostate cancer has been discovered well before the effective filing date of the instant application. That discovery has been used in the art to make prodrug to target anti-cancer agents specifically to prostate cancers thereby minimizing damaging to normal cell that do not express PSMA. Chemistry linking the

cytotoxic agent to polyglutamate in Pinto et al is not same as the product in the instant application.

However, Liu et al teach the peptide bond between polyglutamate to another peptide via epsilon group of lysine residue has been known since 1970's.

Since Pinto et al suggest that gamma linked polyglutamates could protect normal cells from cytotoxic drugs by inactivating them until they reach the right place, and di-glutamates are a minimum requirement of poly-glutamates and perhaps easiest and cheapest to make if works, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the claimed invention was made to make procytotoxin comprising amoebapore H3 domain modified by linking two gamma linked glutamates through epsilon group of the C-terminal lysine in order to inactivate the cytotoxic amoebapore H3 domain until it reaches target cells, namely prostate cancer cells expressing PSMA which cleaves the gamma linked glutamates and selectively kills prostate cancer cells instead of causing havoc to entire body of the person who has prostate cancer. The state of art is such that making the product (amoebapore H3 domain modified by linking two gamma linked glutamates through epsilon group of the C-terminal lysine) is accomplished with a reasonable expectation of success.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Double Patenting

Claims 1-5, 8, and 9 are provisionally rejected for reason of record and the new claims 20-22 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 12, 13, and 21 of copending Application No. 09/938,623. Applicant request, that this rejection is held in abeyance until other issues are resolved, is granted.

Conclusion

No claim is allowed.

Any other objections and rejections set forth in the Office action mailed on 05-19-2003 are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Karen A. Gamilla

Misook Yu

November 24, 2003